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Manganese testing under a clean air act test rule and the application of resultant data in risk assessments☆

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ABSTRACT

In the 1990′s, the proposed use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an octane-enhancing gasoline fuel additive led to concerns for potential public health consequences from exposure to manganese (Mn) combustion products in automotive exhaust. After a series of regulatory/legal actions and negotiations, the U.S. Environmental Protection Agency (EPA) issued under Clean Air Act (CAA) section 211(b) an Alternative Tier 2 Test Rule that required development of scientific information intended to help resolve uncertainties in exposure or health risk estimates associated with MMT use. Among the uncertainties identified were: the chemical forms of Mn emitted in automotive exhaust; the relative toxicity of different Mn species; the potential for exposure among sensitive subpopulations including females, the young and elderly; differences in sensitivity between test species and humans; differences between inhalation and oral exposures; and the influence of dose rate and exposure duration on tissue accumulation of Mn. It was anticipated that development of specific sets of pharmacokinetic (PK) information and models regarding Mn could help resolve many of the identified uncertainties and serve as the best foundation for available data integration. The results of the test program included development of several unique Mn datasets, and a series of increasingly sophisticated Mn physiologically-based pharmacokinetic (PBPK) models. These data and models have helped address each of the uncertainties originally identified in the Test Rule. The output from these PBPK models were used by the Agency for Toxic Substances and Disease Registry (ATSDR) in 2012 to inform the selection of uncertainty factors for deriving the manganese Minimum Risk Level (MRL) for chronic exposure durations. The EPA used the MRL in the Agency's 2015 evaluation of potential residual risks of airborne manganese released from ferroalloys production plants. This resultant set of scientific data and models likely would not exist without the CAA section 211(b) test rule regulatory procedure.

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1. Introduction

Manganese (Mn) is both an essential dietary nutrient and, depending on factors such as: dose; Mn speciation; bioavailability; route of exposure; and individual susceptibility, a neurotoxicant. Similar to other trace nutrients such as zinc or copper, manganese is required for normal metabolic functions and is an abundant component of a typical healthy diet. The recommended adult daily dietary intake values range from 2 to 5 mg/day (FDA, 2017; NRC, 1989), with 3–10 percent of ingested Mn being systemically absorbed from the gut and elimination largely from the bile into the feces. At high levels of exposure via ingestion or inhalation, homeostatic controls of blood and tissue concentrations are overcome and manganese accumulates in the brain and other

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tissues, with potentially toxic results. Excessive exposure is associated with manganese accumulation in the striatum, globus pallidus, substantia nigra and other brain regions, and dysfunction of the nigrostriatal pathway. Mn accumulation in the globus pallidus region of the brain, in particular, has been the focus of work to understand the relationships between exposure and target tissue accumulation of manganese. The resulting impairments from Mn accumulation in the globus pallidus, a component of the basal ganglia, and other brain regions include a variety of mood and cognitive changes, and marked extrapyramidal motor signs that resemble idiopathic Parkinson's disease, but are distinct in the pathophysiology and responsiveness to dopaminergic pharmacotherapies.

1.1. MMT as a fuel additive

Manganese has a variety of uses in industry and commerce including steel production, welding, and as a component of some fungicides. The EPA recognized a potential public health concern from more widespread exposure to manganese through the proposed use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an octane-enhancing fuel additive. MMT had been used in gasoline and other fuels to enhance octane and improve anti-knock performance since the 1950s. The Clean Air Act (CAA) and its amendment in 1977 requires fuels and fuel additives to be registered with EPA. In the mid-1970s the removal of lead from automotive fuel, an oil embargo that caused fuel shortages in the US, and other factors led to a proposal by the Ethyl Corporation (currently known as Afton Chemical) to register MMT as a fuel additive for unleaded gasoline in the US. This proposal generated concerns among the general public and public health authorities regarding the introduction of what was viewed as another neurotoxic heavy metal to gasoline to replace the lead that was being phased out. A series of petitions and legal actions ensued, lasting for nearly two decades (Davis, 1998a, 1998b). Ultimately, the Ethyl Corporation won the legal right to market MMT in the US as a gasoline fuel additive, but with the provision that a series of research studies be conducted under a CAA Section 211(b) Alternative Tier 2 Test Rule regarding the emissions and potential health implications of MMT (Davis, 1998b, 1999).

Currently, although MMT is still a registered gasoline fuel additive, its use is prohibited in US reformulated gasoline with ethanol and in the state of California. Given the wide use of ethanol (which is high octane) in the US due to the Renewable Fuels Standard (RFS) program, the US market for other octane boosters such as MMT is very limited. MMT is marketed as a gasoline fuel additive, however, in a number of countries outside of the US.

1.2. The EPA's reference concentration for manganese

The proposed use of MMT in gasoline in the 1990s prompted EPA to evaluate the potential health risks of exposure to Mn using the best data and risk assessment methodologies that were then available. The EPA's Reference Concentration (RfC) for a substance is intended to represent an airborne concentration within an order of magnitude that would be without adverse health consequences if exposure occurred over a lifetime, and to be protective of sensitive members of the population. The RfC for Mn was based on data from an occupational study (Roels et al., 1992) of male Belgian alkaline-battery plant workers exposed to dust containing manganese dioxide (MnO_2), and who showed impaired performance relative to a matched control group on a number of neuromotor tasks reflecting aspects of fine motor control such as visual reaction time, eye-hand coordination and hand steadiness (Davis, 1998a; U.S. EPA, 1993). There was no evidence for carcinogenicity of Mn and it was not classifiable regarding cancer risk. The inhalation route of exposure was the primary pathway of concern for MMT combustion products in exhaust emissions, so the risk assessment focused on the RfC. The lowest observed adverse effect level (LOAEL) was derived from an occupational-lifetime integrated respirable dust (IRD) concentration of MnO_2 (based on 8-h time weighted average occupational exposure multiplied by individual work histories in years) expressed as mg/m^3 x years. The IRD concentrations ranged from 0.040 to 4.433 mg Mn/m^3 x years, with a geometric mean of 0.793 mg/m^3 x years and a geometric standard deviation of 2.907. A LOAEL was obtained from the Roels et al. (1992) study by dividing the geometric mean integrated "respirable dust" concentration (0.793 mg/m^3 x years) by the average period of worker exposure (5.3 years) to eliminate time (in years) from the time-weighted average, thereby yielding 0.15 mg/m^3. The "respirable dust" was defined as the median of 5 μm from personal samplers based on the Johannesburg's curve for the cohort. The geometric mean concentration was used to represent the average exposure because the workers' exposure measurements were approximately log-normally distributed, and the arithmetic mean exposure period was used because it was the only average value reported in the study (Davis, 1998a). In addition to the use of a respirable faction, a default dosimetric adjustment was applied to account for differences in the approximate volume of air breathed during an 8 h/day work schedule (10 m^3), in relation to a member of the general population potentially breathing air containing Mn around the clock (20 m^3). A duration adjustment was also applied to account for the 5 day/week versus the 7 day/week exposure to the general population. The resulting point of departure for the RfC was 0.05 mg/m^3 (0.15 $mg/m^3 \times 10\ m^3/20\ m^3 \times 5$ days/7 days).

On this value, uncertainty factors (UFs) were applied to reflect a lack of sufficient information regarding protection of sensitive members of the population (10×), using a LOAEL instead of a No Observable Adverse Effects Level (NOAEL) (10×), and a composite UF (10×) reflecting database inadequacy and subsuming extrapolation from subchronic to chronic exposure (including a concern for aged), inadequate data of potential sensitive outcomes such as developmental toxicity, and unknown differences in toxicity among different forms (speciation) of manganese. From the point of departure, therefore, after dividing by a composite UF of 1000, the RfC was established as $(0.05\ mg/m^3)/1000 = 5 \times 10^{-5}\ mg/m^3$ (i.e., 0.05 $\mu g/m^3$).

1.3. Alternatives to the RfC and an MMT exposure assessment

The establishment of an RfC for Mn of 0.05 $\mu g/m^3$ (U.S. EPA, 1993) was followed a year later with an exposure assessment for the use of MMT in gasoline (U.S. EPA, 1994), which included a set of alternative derivations of the RfC using several dose-response models of the data from Roels et al. (1992) to explore the response and it's variability, as well as an estimate of the potential Mn exposure to the population. The alternative estimates of the RfC using benchmark dose and Bayesian models provided estimates ranging between approximately 0.09 and 0.2 $\mu g/m^3$ (Davis, 1998b, 1999; U.S. EPA, 1994). The alternative derivations of the RfC, however, were never incorporated into an updated peer-reviewed risk assessment and the official RfC for Mn remains at 0.05 $\mu g/m^3$.

The EPA's 1994 exposure assessment, based on data from Riverside California in 1990 (where MMT was used in gasoline), contained several assumptions, including that MMT would be present at the maximum legal concentration of 0.031 g Mn/gallon in 100% of the automobile gasoline nationwide (Davis, 1998b, 1999). The Riverside study exposure estimate was only conducted in the spring season in one location, leading to uncertainties regarding other seasons of the year and how representative Riverside would be of other geographic locations. In addition, the assumption that MMT would be used at the full legal concentration

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